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REVIEW

Mechanisms of non-pharmacologic adjunct therapies used during exercise in COPD

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Summary
Individuals with chronic obstructive pulmonary disease (COPD) are often limited in their ability to perform exercise due to a heightened sense of dyspnea and/or the occurrence of leg fatigue associated with a reduced ventilatory capacity and peripheral skeletal muscle dysfunction, respectively. Pulmonary rehabilitation programs have been shown to improve exercise tolerance and health related quality of life. Additional therapeutic approaches such as non-invasive ventilatory support (NIVS), heliox ($He-O_2$) and supplemental oxygen have been used as non-pharmacologic adjuncts to exercise to enhance the ability of patients with COPD to exercise at a higher exercise-intensity and thus improve the physiological benefits of exercise. The purpose of the current review is to examine the pathophysiology of exercise limitation in COPD and to explore the physiological mechanisms underlying the effect of the adjunct therapies on exercise in patients with COPD. This review indicates that strategies that aim to unload the respiratory muscles and enhance oxygen saturation during exercise alleviate exercise limiting factors and improve exercise performance in patients with COPD. However, available data shows

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significant variability in the effectiveness across patients. Further research is needed to identify the most appropriate candidates for these forms of therapies.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a pulmonary disorder that is characterized by progressive irreversible airflow limitation resulting from alveolar wall destruction, bronchiolar narrowing[1] and airway inflammation that occurs in response to inhalation of noxious particles or gases.[2] Although numerous genetic, occupational, and environmental factors have been associated with COPD,[3–5] cigarette smoking remains the primary cause of the disease.[6] COPD is a major cause of morbidity and mortality and poses a substantial economic and social burden worldwide.[1,2]

Individuals with COPD commonly exhibit a limited ability to perform exercise.[2,7,8] Compared to healthy individuals, patients with COPD demonstrate lower maximum exercise capacities and lower levels of peak oxygen consumption (VO_{2peak}),[9–11] with the lowest levels observed in patients with more severe COPD.[10–12] Although moderate correlations between VO_{2peak} and the force expiratory volume in the first second (FEV_1) have been reported in patients with mild ($r = 0.69$), moderate ($r = 0.65$), and severe ($r = 0.87$) COPD, others have found FEV_1 to be a poor predictor of exercise capacity.[13–15] Patients with COPD typically experience dyspnea during exercise; however, the locus of symptom limitation (i.e., the reason for stopping exercise) is not uniform across patients.[16] Whereas the majority patients with COPD stop exercise because of dyspnea, others are limited by leg fatigue or a combination of dyspnea and leg fatigue. Compared to individuals with mild COPD, those with moderate-to-severe disease tend to perceive dyspnea more intensely than leg fatigue.[17] However, patients with COPD also exhibit skeletal muscle abnormalities, which can contribute to exercise intolerance.[18] Although the exact proportion varies among studies, leg fatigue has been reported as the primary symptom limiting exercise during cycling in approximately one third of the patients with COPD.[17,19] Some studies have also reported a moderate correlation between leg discomfort during exercise and the magnitude of contractile muscle fatigue in patients with COPD.[19,20]

In an effort to help reduce dyspnea and improve exercise capacity, individuals with COPD are often referred to pulmonary rehabilitation programs.[21–24] Such programs typically use a multidisciplinary approach, combining education and exercise to optimize physical and social performance and autonomy. However, exercise training has been shown to be the essential component for improving exercise capacity and health related quality of life (HRQoL).[21–23,25–28] The physiological benefits associated with high intensity exercise training include a reduction of exercise lactic acidosis and heart rate for a given work rate,[29] which in turn leads to a lower ventilatory demand and a more effective breathing pattern,[30] enhanced activity of mitochondrial enzymes and capillary density in the trained muscles,[30,31] as well as enhanced anabolic processes in the peripheral muscles.[32] There is also some evidence that whole body aerobic exercise training may improve respiratory muscle function in patients with COPD, as demonstrated by an increase in the maximum inspiratory muscles pressure.[33–35] While low intensity exercise training has also been shown to be effective in improving exercise tolerance with regard to endurance for activities such as walking, it does not lead to the same physiologic training effect that can result from high intensity training.[29] Although studies suggest that

most patients with COPD can benefit from pulmonary rehabilitation,[2,27,29,30,36,37] some individuals with severe lung disease may be unable to obtain a true physiological training effect because of their inability to exercise at a high enough exercise-intensity (i.e., 80% of maximum).[2,29]

Therapeutic approaches such as non-invasive ventilatory support (NIVS),[22,38,39] low-density gases (i.e. Heliox),[40,41] and supplemental oxygen (O_2)[42,43] have been used as non-pharmacologic adjuncts to exercise training to enhance the ability of patients with COPD to exercise at a higher exercise-intensity and thus improve the physiological benefits of exercise.

The current review examines the factors that contribute to exercise limitation in COPD and the physiological mechanisms via which non-pharmacologic adjunct therapies may improve exercise tolerance. Understanding how these adjunct therapies affect the factors contributing to exercise limitation is of paramount importance for guiding identification of the most appropriate forms of therapy for improving exercise in such individuals.

Exercise limitation in COPD

Ventilatory limitation and work of breathing

The changes that occur to the mechanical properties of the lungs in COPD contribute to an increased work of breathing[44,45] and impaired gas exchange.[2] Expiratory flow limitation resulting from airway inflammation and loss of lung elasticity[46] leads to air trapping within the lungs which increases the end-expiratory lung volume (i.e. static pulmonary hyperinflation).[47–49] During exercise, minute ventilation (V_E) is increased predominantly by an increased respiratory rate (RR), whereas tidal volume (V_T), which approaches the limits of total lung capacity at end-inspiration, increases marginally before reaching a plateau (Fig. 1).[50] The increased RR results in less time available for exhalation, and leads to further increases in end-expiratory lung volume (i.e. dynamic hyperinflation).[49–52] Because the respiratory system is less compliant at higher lung volumes, static and dynamic hyperinflation contribute to an increase in the inspiratory elastic work of breathing. This is further compounded by an

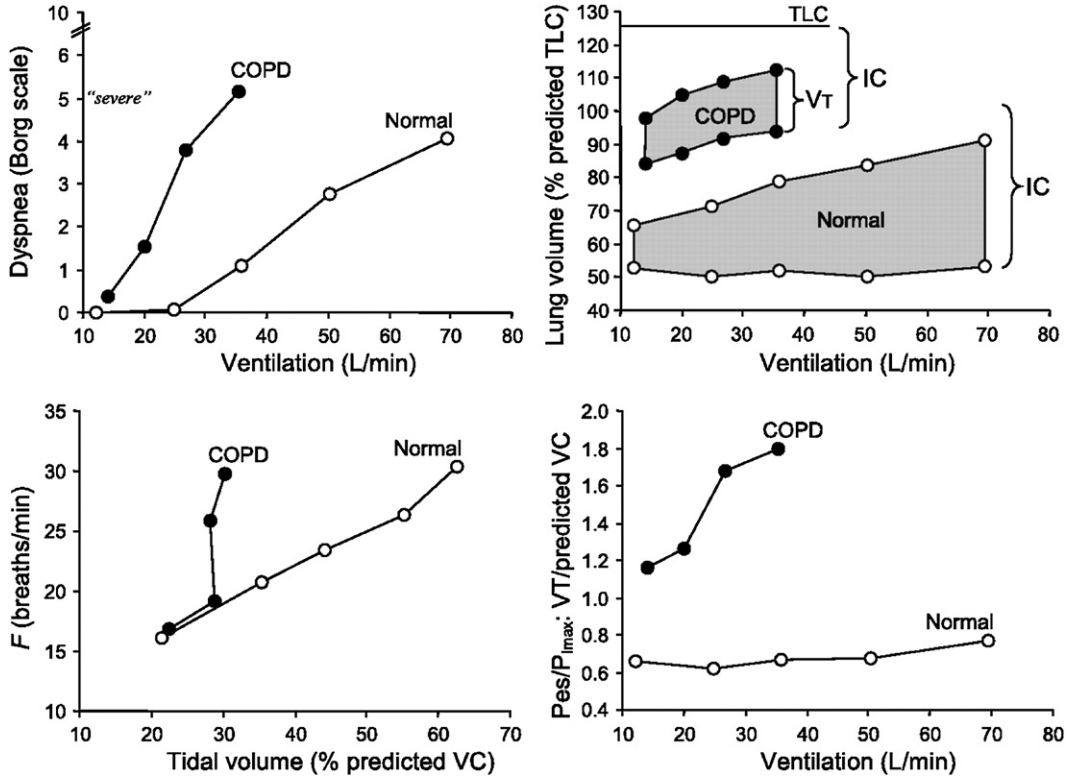

Figure 1 Ventilatory response to incremental exercise is shown in patients with COPD and in age-matched healthy individuals. Changes in dyspnea intensity (upper left), operational lung volumes (upper right), breathing pattern (lower left) and the effort-displacement ratio (lower right) are shown as ventilation increases with exercise. Dyspnea intensity is greater and breathing pattern is more rapid and shallow in COPD (solid circles) compared to healthy individuals (open circles). Greater mechanical constraints on tidal volume (VT) are evident in COPD because of increasing end-expiratory ling volumes and limitation from above by the total lung capacity (TLC). To increase ventilation, individuals with COPD increase breathing frequency (F) to a greater extent. Tidal inspiratory pressure swings expressed as a fraction of their maximal force-generating capacity (P_{es}/PI_{max}) relative to the VT response expressed as a fraction of the predicted vital capacity (VC) show a significantly steeper slope in COPD.[8] Reprinted with permission of the American Thoracic Society. Copyright (©) 2012 American Thoracic Society. Official Journal of the American Thoracic Society.

inspiratory threshold load whereby patients with COPD must often generate an inspiratory threshold pressure before airflow occurs, i.e. intrinsic positive end-expiratory pressure (PEEPi).[53]

The development of hyperinflation additionally decreases inspiratory muscle length, which reduces the ability of such muscles to generate force.[54] Dynamic hyperinflation therefore contributes to neuromechanical uncoupling whereby an increased inspiratory effort is required to generate a given ventilatory output. Under conditions of impaired length—tension relationship[54] and reduced coupling, COPD patients need to increase central respiratory drive and diaphragm activation[55—57] in order to maintain the same pressure generated across the diaphragm (i.e. transdiaphragmatic pressure)[57] (Fig. 2). This increased activation has been associated with greater respiratory effort sensation,[48,50,56] increased energy demands,[58,59] as well as enhanced inspiratory muscle fatigability.[57,58,60,61]

Peripheral muscle dysfunction

In addition to the clear evidence of dynamic hyperinflation and altered pulmonary mechanics contributing to exercise intolerance in COPD, peripheral muscle dysfunction also appears to play an important role in limiting exercise in such individuals.[2,17,62]

The skeletal muscle abnormalities that occur in COPD result from both deconditioning[63] secondary to decreased activity levels,[31] and from systemic inflammation.[64,65] These abnormalities are characterized by a reduction in the proportion of type I fatigue-resistant fibers,[66,67] increased proportion of less efficient type II fibers,[68,69] reduced cross-sectional area of type I fibers i.e. muscle atrophy,[66,68] and a reduced oxidative enzyme activity.[70] Several studies have shown a relationship of such changes with reduced peripheral muscle strength and endurance, as well as an increased contractile fatigability.[62,68,70,71] Contractile muscle fatigue has been defined as a reversible reduction in the capacity of the skeletal muscle to generate force in response to a given neural input.[72,73] Evidence for the occurrence of quadriceps contractile fatigue during exercise in patients with COPD comes from several studies that have assessed quadriceps muscle strength via magnetic stimulation.[74—78] Studies have shown quadriceps strength to be correlated with maximum exercise capacity, independent of pulmonary function.[71,77,79] Saey et al.[77] demonstrated that even after an improvement in FEV_1 following bronchodilator medication, quadriceps contractile fatigue was still evident following endurance cycling in a subgroup of patients who previously reported leg fatigue as being the primary factor limiting maximum exercise. These findings suggest that the presence of leg fatigue modulates the exercise response to bronchodilation.

Although muscle fatigue is a complex phenomenon, changes in muscle energy metabolism may be involved.[77] Several studies have found that compared with age-matched healthy individuals, COPD patients have lower lactate thresholds (i.e. VO_2 at which blood lactic acid begins to increase).[63,80] The lower lactate thresholds lead to an excessive accumulation of metabolic by-products during exercise,[29,81] which further impairs contractility

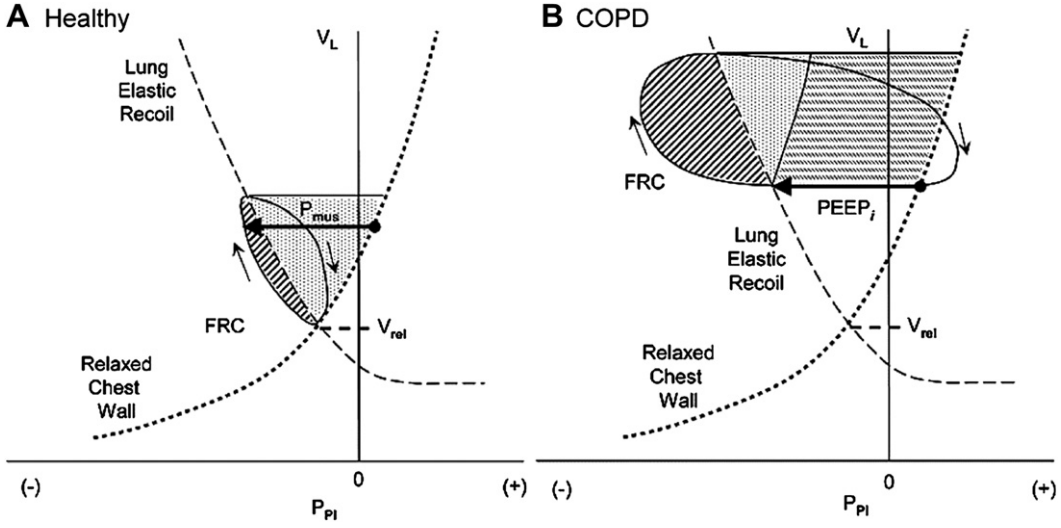

Figure 2 Campbell diagram showing the volume of lung or chest wall (V_L) plotted against pleural pressure (P_{PI}) and the effects of dynamic hyperinflation on inspiratory muscle work. FRC: functional residual capacity. The continuous line (loop) traces a complete breath from FRC; arrows show direction. The dashed line shows the elastic characteristic of the lung (negative of elastic recoil pressure), and the dotted line shows the elastic characteristic of the relaxed chest wall. P_{mus}, pressure change generated by inspiratory muscles (length of the horizontal arrow). PEEPi, intrinsic positive end-expiratory pressure that must be overcome before inspiratory flow can begin (length of the horizontal arrow). The diagonally hatched area is work done against resistance, stippled area is work done against elastance of lung and chest wall, and horizontally hatched area is work to overcome PEEPi. (A) Illustrates the FRC is equal to V_{rel}, the relaxation volume of the respiratory system in a healthy individual, and (B) FRC is increased above relaxation volume in an individual with COPD. In COPD, the work done against inspiratory resistance is increased whereas the elastic characteristics of lung and chest wall are unchanged. Ref. 53.

and increases the risk of fatigue in patients with COPD.[18] The increased CO_2 production also further increases the ventilatory demand and induces ventilatory limitation at lower than normal exercise workloads,[82] thus causing early exercise termination in such patients.[2,7,17]

Cardiac function and blood distribution

Cardiac output (CO), which is the body's energy supply and the product of stroke volume and heart rate (HR) is regulated principally by the demand for O_2 by the cells of the body.[83] In general, the exercise-induced increase in VO_2 is achieved by an increased CO and an increased O_2 extraction at the level of the working respiratory and peripheral skeletal muscles. During both sub-maximal and maximal exercise in healthy individuals, CO increases nearly linearly with VO_2, suggesting that O_2 consumption is linearly related to the energy supply.[84–86] Although COPD patients likewise present an almost linear CO and VO_2 relationship during sub-maximal exercise,[87–89] HR has been reported to be higher than normal at any given VO_2,[90] implying that stroke volume (SV) is lower than normal.[91] In the absence of coexisting left-sided heart disease, evidence suggests that the decreased SV occurs secondary to reduced right ventricular ejection fraction at rest and which, on average, fails to increase with exercise among patients with COPD.[92–94] As with CO, blood flow to the exercising peripheral muscles at a given sub-maximal exercise work rate is similar in patients with COPD and healthy individuals.[11,81] In contrast, individuals with COPD reach lower peak exercise work rates and exhibit a reduced peak VO_2 (30–50% lower) and peak CO (35–60% lower) with a normal or reduced HR, as well as a lower peak leg blood flow compared to healthy individuals.[9–11,87–89,95–97]

Dynamic hyperinflation appears to have a significant impact on cardiovascular function during exercise in patients with COPD.[91] Vassaux et al.[98] showed a strong association ($r = 0.87$) between inspiratory-to-total lung capacity ratio (IC/TLC represents an index of hyperinflation) at rest and exercise and O_2 pulse (i.e. VO_2/HR, a surrogate marker of cardiac function), demonstrating that the most hyperinflated patients (i.e. IC/TLC $\leq 0.25\%$, an indicator of severe static hyperinflation), had a lower peak exercise O_2 pulse at a similar work load than patients having less hyperinflation (i.e., IC/TLC $> 0.25\%$).[98] In an attempt to maintain the required ventilation during exercise when the ability to increase O_2 supply is limited, individuals with severe hyperinflation are forced to generate a larger intra-thoracic pressure.[92,99] This in turn, limits venous return, right and left ventricular (LV) blood volumes, and consequently, cardiac output.[92,100,101] In addition, loss of pulmonary vascular capacity with emphysema results in an increased pulmonary vascular resistance which may ultimately impair LV filling. Barr et al.[101] reported that the severity of airflow obstruction (FEV_1/FVC) and the degree of emphysema on chest CT scans was inversely correlated with reductions in LV end-diastolic volume, stroke volume and CO. Although there was a stronger association in more severe patients, hemodynamic changes also occurred with mild emphysema and airflow obstruction. Watz et al.[102] reported that IC/TLC was more strongly correlated with cardiac chamber size than measurements of airway obstruction or diffusion capacity, and that COPD patients with IC/TLC $\leq 0.25\%$ not only have an impaired LV filling, but also a reduced functional capacity as indicated by a lower 6-min walk distance.

Several studies have suggested[10,103–105] that when the energy demands of the respiratory muscles are increased, such as during exercise, a competition for blood flow develops between the respiratory and peripheral muscles, which ultimately favors a redistribution of blood flow from the locomotor to the respiratory muscles. Evidence for this phenomenon, known as the "respiratory steal" or "blood stealing effect",[103] comes from Simon et al.,[106] who found that about 45% of the patients with COPD participating in their study demonstrated a leg blood flow plateau during whole body incremental cycling exercise, despite increasing exercise work load. They additionally found that the patients who exhibited such a leg blood flow plateau also revealed a greater work of breathing at sub-maximal exercise, indicating a high O_2 demand of the respiratory muscles.[106] In this context, it has been suggested that reduction in blood flow to the working peripheral muscles may induce leg fatigue, thereby limiting the duration and the intensity of exercise in patients with COPD as demonstrated by other studies.[82,107]

Non-pharmacologic adjunct therapies

In the last several years, adjunct therapies to exercise training such as non-invasive ventilatory support and heliox have been investigated in an attempt to counter the high respiratory muscle workloads experienced by patients with COPD during exercise. It is anticipated that by unloading the inspiratory muscles, such strategies might enable individuals to exercise at higher intensities, thereby increasing also the training load to the peripheral muscles and enhancing the physiologic benefits of exercise training.

Non-invasive ventilatory support

Although non-invasive mechanical ventilation has traditionally been used with patients who have respiratory failure or sleep apnea,[108,109] it has recently gained more attention as a potential tool for increasing exercise tolerance during pulmonary rehabilitation in patients with COPD.[110] Non-invasive ventilatory support (NIVS) differs from traditional invasive mechanical ventilation, by the fact that it does not require the patient to be intubated (i.e. endotracheal or nasotracheal tube) for delivery of the positive pressure.[111] NIVS can be delivered through a variety of interfaces such as a mouthpiece, nasal prongs, or facemask.[39,112,113]

The modes of mechanical ventilation that have been used for the delivery of NIVS during exercise include: (1) continuous positive airway pressure (CPAP), which delivers a constant positive pressure that elevates the baseline pressure (airway pressure which is constantly higher than atmospheric pressure)[38,114]; (2) bilevel positive airway pressure (BiPAP) provides continuous positive pressure at two levels, a higher one for inspiration (IPAP) and a lower for expiration (EPAP), where both are above atmospheric

pressure, and the difference between IPAP and EPAP is a reflection of the amount of pressure support provided to the patient[115–122]; (3) pressure support ventilation (PSV),[123–127] which is a pressure-targeted mode whereby each breath is patient triggered and cycled; and (4) proportional assist ventilation (PAV)[128–132] which provides assist in proportion to the patient's spontaneous effort, according to the equation of motion (requiring the determination of elastance and resistance and instantaneous measures of flow and volume). This requires that the pressure that is delivered within a breath is continuously readjusted in proportion to the pressure that is generated by the inspiratory muscles, determined using instantaneous measurements of inspiratory airflow and volume.[128]

Effect of NIVS on respiratory and peripheral muscles and their interaction

There is evidence that NIVS unloads the inspiratory muscles and reduces the work of breathing both at rest and during exercise.[127,133,134] NIVS has also been shown to decrease dyspnea, and increase endurance time in individuals with moderate-to-severe COPD.[38,103,127,129,135,136] Previous studies have demonstrated a relationship between decreased dyspnea and reduced work of breathing[127,135,136] as well as decreased dyspnea and diaphragm deactivation.[137] Unloading the respiratory muscles during high-intensity exercise (70–80%Wmax) using NIVS has also been found to improve peripheral muscle oxygenation[117,138] and to reduce blood lactate levels[129,139] which in turn not only reduces the occurrence of leg fatigue, but also further decreases respiratory drive and dyspnea,[129,139] and thereby has the potential to decrease ventilatory limitation to exercise.

Several studies have demonstrated that NIVS administration during exercise increases V_E as a result of both increased V_T and RR[127,129] or only V_T,[38] whereas others have reported no change in V_E for a given work load.[103,125,135,140] There is evidence, however, that NIVS promotes a reduction in inspiratory work load, whether[127] or not[135] V_T and end-inspiratory lung volume are increased.[133,141] Although NIVS has no direct effect on end-expiratory lung volume,[38,133,141] PSV during exercise has been reported to promote greater diaphragm muscle deactivation in patients with COPD compared to healthy individuals,[133] supporting the unloading effect of NIVS.

In patients with more severe COPD, up to 50% of the whole body VO_2 during exercise goes to the respiratory muscles due to an increased work of breathing,[142] enhancing the likelihood of the occurrence of the respiratory steal phenomenon.[10,103] Several lines of evidence suggest that reducing the work of breathing via NIVS may decrease ventilatory muscle blood flow requirements and allow a fraction of the limited CO to be redirected to the locomotor muscles, thereby improving peripheral muscle perfusion, and in turn exercise capacity.[103,143] These responses to NIVS have been found to improve endurance time in both healthy individuals[104,105] and patients with COPD.[117,138]

The effects of NIVS on the cardiac performance are complex, with most resulting from an NIVS associated rise in mean intra-thoracic pressure and a fall in transmural pressure.[134,144–146] In a study evaluating the effect of PSV+PEEP, Oliviera et al.[138] showed that NIVS promoted an increase in stroke volume, HR, CO, and ultimately exercise endurance in one subgroup of COPD patients; however, in another subgroup, NIVS resulted in a decreased stroke volume and HR, thereby reduced CO with no improvement in exercise endurance. The study found that patients in the latter subgroup tended to be more hyperinflated, suggesting that NIVS may have a deleterious effect on hemodynamics and exercise tolerance in COPD patients who exhibit greater static hyperinflation.

Although there is no evidence to date supporting the use of one mode of NIVS over another, PAV has been advocated for exercise training because it is believed to enhance the synchrony between patient effort and ventilatory support[128,147] thus improving patient comfort, reducing dyspnea and increasing exercise tolerance.[129,130] However, the need for continuous measurement of the patient's respiratory mechanics (i.e., resistance, elastance, and iPEEP) and adjustment of ventilator settings greatly increases the complexity of this mode of mechanical ventilation.

From the accumulated evidence, there is ample empirical data showing that NIVS applied during exercise unloads the inspiratory muscles, decreases the drive to breathe thereby reducing dyspnea, delays lactate buildup, and ultimately improves exercise performance among patients with COPD. Such improvements, however, vary considerably among individuals. Moreover, there is inconsistent data corroborating the use of NIVS during routine pulmonary rehabilitation programs for increasing the overall benefit of pulmonary rehabilitation compared to training alone.[132] Discomfort to ventilator settings and/or the interface used to deliver the assist[120] are factors that may contribute to lack of tolerance to NIVS, and thus compliance to the exercise program. NIVS delivery during exercise is labor intensive and may consequently increase the cost of the pulmonary rehabilitation program. NIVS should therefore only be considered in selected patients with COPD who demonstrate acute benefits from this intervention.

Heliox

The complex configuration of the bronchial tree, together with its branching angles and the internal airway diameter with its degree of roughness causes airflow to change from a turbulent to a laminar flow pattern as air moves from the central to the conductive and peripheral airways.[148,149] Turbulent flow is further increased in patients with COPD consequent to airway inflammation and a loss of alveolar tethering, which causes narrowing of the airways. The resultant effect in such patients is an increased airway resistance and increased work of breathing at rest that becomes even more prominent during exercise.[150]

Breathing a low-density gas mixture, such as normoxic heliox ($He–O_2$) – a mixture of 79% helium and 21% O_2 (79% He–21% O_2), decreases airway resistance by maintaining or re-establishing laminar flow within the tracheobronchial tree at higher flow rates.[151–157] Similar to NIVS, heliox can be delivered non-invasively using different delivery

methods with a variety of patient interfaces such as a mouthpiece or facemask. The gas mixture is available in tanks of different sizes, with the 50l tank being the most frequently used. The tanks are pressurized at approximately 200 bar for a normoxic He—O_2 mixture, and the air regulators are connected to the ventilator[156] from which the mixture is delivered to the patient.

Effect of heliox on respiratory and peripheral muscles and their interaction

The administration of heliox, which is approximately three times less dense than air, during exercise in individuals with airflow obstruction has been shown to reduce resistive work of breathing and increase maximum expiratory flow, thus promoting faster lung emptying.[40,158] In addition, evidence shows that heliox breathing increases V_E during exercise[40,152,159—162] and also improves exercise tolerance,[40,152,159,161,162] while reducing dynamic hyperinflation and dyspnea at isotime.[41,152,159,160,162] This indicates that heliox is able to alleviate dyspnea and the work of breathing by primarily reducing ventilatory constraints.[40,41,152,162] Using esophageal and gastric balloon catheters, Vogiatzis et al.[160] recently demonstrated the positive effect of heliox on reducing the work of the inspiratory and expiratory muscles during exercise.[160]

There is emerging evidence which suggests that heliox-induced respiratory muscle unloading also improves distribution of the CO to the peripheral muscles during bicycle exercise in COPD patients.[10,103,159,160] Richardson et al.[10] showed that heliox administration promoted an increased VO_{2peak} and peak work load during whole body cycling exercise, with no change in arterial O_2 saturation, suggesting that the VO_2 increased secondary to enhanced peripheral O_2 availability and improved perfusion of the peripheral muscles.

Respiratory muscle unloading via heliox administration has also been associated with an improved O_2 delivery and extraction in the exercising locomotory muscles in moderate-to-severe COPD.[40] The increase in peripheral muscle O_2 delivery has been assumed to result from a redistribution of blood flow from the respiratory to the leg muscles.[10,40] Interestingly, a recent study found that heliox breathing during near-maximum exercise (i.e., 75% peak work load) improved both quadriceps and intercostal muscle O_2 delivery due to an increase in both arterial O_2 content and quadriceps and intercostal muscle blood flow in patients with moderate-to-severe COPD with static but not dynamic hyperinflation.[160] In contrast to the previous studies, these findings do not support the "respiratory steal" phenomenon. Instead, it was concluded that the increased muscle blood flow and perfusion was due to a reduction in the work performed by the respiratory muscles.

In addition to the normoxic heliox, the effects of different O_2 concentrations (hyperoxia) in the heliox gas mixture have also been investigated. In these studies, improvement in exercise performance was associated with increased ventilatory capacity and decreased dynamic hyperinflation[152] and dyspnea.[41,152] These studies indicate that compared to either normoxic heliox or hyperoxia alone, administration of a combination of helium and hyperoxia may provide a greater effect in reducing dynamic hyperinflation and work of breathing (WOB) and improving exercise performance.

Heliox breathing, similar to NIVS, unloads the respiratory muscles and relieves both dyspnea and leg discomfort during exercise. This allows COPD patients to exercise longer prior to exhaustion and enhances the physiological training effect,[162] which in turn, could ultimately result in an improved activity of daily life and HRQoL.[41,160] Despite the current findings, the overall cost of the ventilator set-up and the gas mixture makes the use of this therapy cumbersome/impractical and/or too expensive to be incorporated into routine pulmonary rehabilitation programs or training at home. Notwithstanding the evidence to support the use of heliox as an adjunct to exercise, further studies are needed to identify those individuals most likely to benefit from this intervention. Furthermore, studies are needed to determine the long-term utility of heliox during rehabilitation programs in COPD patients and determine how best to incorporate the latter into routine clinical practice.

Supplemental oxygen

In certain individuals with COPD, ventilation-perfusion mismatch and hypoventilation,[163] can lead to impaired gas exchange and hypoxemia[164] at rest and/or during exercise.[112,165] Studies have shown that in patients with severe COPD, even routine daily activities such as walking, stair-climbing, washing, or eating can induce hypoxemia.[166,167] Hypoxemia stimulates ventilatory drive, with the goal of increasing V_E, lowering $PaCO_2$ and in turn causing vasodilatation of the vascular bed, tachycardia, and an increased CO.[112,168] Chronic hypoxemia can additionally lead to pulmonary hypertension and cor pulmonale (i.e. right heart failure), thereby reducing CO and impairing O_2 delivery.[169] With these factors compounding the effects of hyperinflation, it becomes evident that the hypoxemic patient with COPD is especially susceptible to lactic acidosis, muscle fatigue and reduce exercise capacity.[112,169]

Effect of supplemental oxygen on the ventilatory and peripheral muscles and their interaction

Administration of supplemental O_2 during exercise to patients with COPD who are hypoxemic at rest and/or who desaturate with exercise has been shown to reduce V_E[170], RR and ventilatory drive[171—173] for a given exercise work load. The lower V_E which occurs secondary to a lower RR, has been reported to promote a reduction in dynamic hyperinflation,[172] thus placing the diaphragm on a more optimal contractile portion of its length—tension curve. O_2 supplementation in hypoxemic patients has been reported to improve the diaphragm's ability to sustain dynamic work,[174] to increase exercise endurance and to delay the onset of respiratory muscle fatigue[175] and dyspnea.[176] Interestingly, the association between increased endurance time with supplemental O_2 and the delayed onset of diaphragmatic fatigue has also been found in several studies that examined healthy individuals breathing against

an inspiratory resistance.[177,178] While some authors have suggested that the lower V_E that occurs with supplemental O_2 is related to slower ventilatory kinetics in such hypoxemic patients,[171] others have attributed the decreased V_E to delayed lactate accumulation, secondary to an increased peripheral muscle O_2 delivery, both in hypoxemic[179]and non-hypoxemic patients.[180] Evidence for the latter comes from a strong correlation between the decrease in V_E and fall in lactate accumulation ($r = 0.88$, $p = 0.001$).[179]

Similar to the findings in hypoxemic patients, several studies have likewise reported reductions in the RR, V_E,[42] respiratory drive and dynamic hyperinflation[42,43,180] along with improvements in exercise tolerance[180,181] in normoxic COPD patients receiving supplemental O_2 during exercise. The mechanism linking reduced respiratory drive and improved exercise tolerance is said to be the prolongation of expiratory duration which reduces dynamic hyperinflation and the elastic work of breathing.[42,43,180] In addition, it was shown that the decreased ventilation observed with supplemental O_2 during exercise in normoxemic patients resulted is an increased mean femoral O_2 delivery, suggesting that a part of the blood flow may have been redistributed from the ventilatory to the peripheral muscles.[182] However, the increased peripheral muscle blood flow during exercise may not necessarily be the result of a blood flow redistribution mechanism, since a concomitant increased inspiratory muscle blood flow has also been found with adjunct therapies that decrease the work of breathing, suggesting that other factors/mechanisms may be implicated.[160] Interestingly, Siqueira et al.[183] recently showed that despite improved central O_2 delivery and blood oxygenation with supplemental O_2 administration, some normoxemic COPD patients do not benefit from O_2 supplementation during exercise due to an impaired intramuscular O_2 utilization.

Although the current evidence demonstrates that supplemental O_2 can improve O_2 saturation and peripheral tissue oxygenation, reduce dyspnea, and increase exercise capacity in both hypoxemic and non-hypoxemic COPD patients, the effects vary considerably among individual patients. Interestingly, Emtner et al.[42] found that non-hypoxemic patients, who acutely improved exercise tolerance with supplemental O_2, benefited more from using this therapy during exercise training in a pulmonary rehabilitation program. However, use of supplemental O_2 during exercise training for non-hypoxemic patients is not routine clinical practice at this point in time.

Conclusion

Although considerable research has been devoted to the effect of adjunct therapies for exercise training that may be useful in pulmonary rehabilitation programs, less is known about which patients are most likely to benefit from them. Reducing the work of breathing, dyspnea and peripheral muscle fatigue in patients with COPD is a key mechanism for improving exercise tolerance and activity. In the current review, three physiologically based interventions able to improve exercise tolerance have been discussed. It should be noted, however, that none of these therapies is currently routinely used in the context of pulmonary rehabilitation, apart from supplemental O_2 for patients who have resting and/or exercise-induced O_2 desaturation, given that none has been proven to improve overall magnitude and/or duration of gains made in the context of routine clinical pulmonary rehabilitation programs. Although the administration of non-invasive ventilatory support, heliox and supplemental O_2 during exercise have been shown to unload the inspiratory muscles, reduce breathlessness, and enhance exercise endurance in patients with moderate-to-severe COPD, current available data demonstrates significant variability in their effectiveness across patients. Whether or not the symptoms limiting exercise contribute to such variability is unknown, raising the question whether patients who are limited by dyspnea obtain greater benefits from these adjunct therapies during exercise than those who are limited by leg fatigue. We propose that these techniques should be targeted towards individuals who show the most promising response. Examination of the acute effects of these adjunct therapies on exercise may provide insight into why some patients experience a greater benefit in use of these adjunct therapies during exercise training than others and may help to identify the most appropriate candidates for these forms of therapy.

Conflict of interest

None of the authors, A.M.M., M.d.M., D.S., and J.S, have any financial or other relationships that would constitute a conflict of interest.

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